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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,013	10/09/1998	TIMOTHY H. BESTOR	48075-B-PCT	7512

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/051,013	BESTOR, TIMOTHY H.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-15,18,24-26 and 42-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-15,18,24-26 and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 23, 2004 has been entered.

[2] Claims 1-8, 10-15, 18, 24-26, and 42-46 are pending in the application.

[3] Applicant's preliminary communication, filed January 23, 2004, is acknowledged. The arguments presented therein have been fully considered and are addressed below.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Oath/Declaration

[5] The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.The oath or declaration is defective because: It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Sequence Compliance

[6] Receipt of a substitute sequence listing in computer readable form, a paper copy thereof, and a statement of their sameness, filed April 10, 2000, is acknowledged. However, the examiner can find no statement that the substitute sequence listing includes no new matter as required by 37 CFR 1.825(a).

Claim Rejections - 35 USC § 112, First Paragraph

[7] The written description rejection of claims 1-8, 10-15, 18, 24-26, and 42-46 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The examiner maintains his position that the specification fails to describe the claimed genus of chimeric proteins and encoding nucleic acids. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. In the instant case, applicant has described the species encompassed by the genus only by functional characteristics, i.e., no structural characteristics of the genus have been described.

Applicants argue that the examiner has failed to show that the specification does not describe the claimed invention. Applicants argue that the examples of the claimed chimeric proteins described in the specification are representative of the variability within the genus based on the assertions that the knowledge and skill in the art is high, that the variation within the genus arises from the combination of known proteins, the knowledge of methyltransferases, DNA binding proteins, and molecular cloning in the prior art. Applicants argue it is not necessary that the specification provide support for all species encompassed by a genus and assert that it is not necessary for the specification to teach the structures of all chimeric proteins in order to satisfy the written description requirement. Applicant argues that the specification, in view of the knowledge and high level of skill in the art, adequately describe the claimed invention. Applicants argue that only a generalized structure of a chimeric protein is required to know what applicant regards as the invention and that one of skill in the art can easily envision any chimeric protein of the genus, in view of the specification. Regarding the mutant methyltransferase, applicant argues that the identity of a particular mutation need not be described. Applicant's argument is not found persuasive.

It is noted that not even a single "representative species" of the claimed genus has been described in the specification. Instead, applicant presents trial and error screening methods for identifying the desired chimeric proteins (see Examples 1 and 3, pages 39-42 and 44-47, respectively, of the specification). The unpredictability and trial and error nature of the screening methods is evidenced by the specification, which states, "[i]t cannot be predicted as to which mutations might give the desired reduction in affinity for DNA, so random mutations are introduced and selection is applied to obtain mutants of the desired character" (page 40, lines 10-14) and acknowledges that such random mutations may not generate a DNA encoding the desired chimeric protein (page 42, lines 4-7). The issue at hand is whether a written description of a claimed genus of chimeric proteins is adequate where the necessary components of the chimeric protein are described only in terms of their functions and where the only means for finding such components is essentially by trial-and-error. The CAFC in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998), stated that "[a]n adequate written description of a DNA ... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly,* 119 F.3d at 1566 (quoting *Fiers*, 984 F.2d at 1171). Nowhere, however, does the specification specify which chimieric proteins have the desired characteristics of having a DNA-methyltransferase whose DNA binding activity is attenuated and having a DNA binding protein that binds to the gene's promoter thereby permitting methylation and thus inhibiting target gene expression (see claim 1) and does not identify any particular chimeric protein or components thereof that the screening methods as set forth at pages 39-42 and 44-47 will identify as suitable for this purpose. Knowing the "starting point" is not enough; that is little more than a research plan. The specification describes how to screen for chimeric proteins to determine whether they successfully inhibit target gene expression, but it does not set forth any procedure that will necessarily lead to the identification of such a chimeric protein. One of skill in the art, reading the specification, would not understand what chimeric protein is necessary to inhibit target gene expression, nor would one know how to find such a chimeric protein except through trial and error, which hardly suggests conception of a complete invention. Section 112, ¶ 1, however, requires the inventor to "show that an invention is complete by disclosure of sufficiently

detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention ...." See MPEP § 2163. See also *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003). MPEP § 2163 states, "[t]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function." In this case, the mutations in the DNA methyltransfease/DNA binding protein moieties of the chimeric protein that result in the protein having the desired characteristics are an essential and critical feature of the claimed invention that have not been described in the specification. For the reasons of record and those stated above, it is the examiner's position that the specification does not provide adequate written description for the claimed invention.

[8] The enablement rejection of claims 1-8, 10-15, 18, 24-26, and 42-46 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. It is noted that the instant rejection was incorrectly identified as a "scope of enablement" rejection in a previous Office action (see item [7] of the Office action mailed December 10, 2003). However, it is clear that the instant rejection is not a "scope of enablement" rejection as the examiner has not identified any enabled subject matter within the scope of the claims and previous Office actions identify the rejection as a complete "enablement" rejection and not a "scope of enablement" rejection (see, e.g., items [8] and [5], respectively, of the Office actions mailed May 16, 2003 and November 05, 2002). The examiner maintains his position that the specification fails to enable the claimed chimeric proteins, encoding nucleic acids, pharmaceutical compositions thereof, and methods of inhibiting gene expression. In this case, undue experimentation is required to make and use the claimed invention.

Applicant argues that given the knowledge in the art of DNA methyltransferases, DNA binding proteins, and chimeric proteins, in combination with the guidance provided by the specification, particularly Examples 1 and 3, one of skill in the art would expect to be able to make and use the entire scope of claimed chimeric proteins. Applicant argues that the specification, particularly Example 1, provides guidance for isolating the mutant methyltransferase with the desired activity and that no knowledge of the specific mutations conferring this activity is required to enable the claimed invention.

Applicant argues Example 1 teaches a novel selection method, which is combined with the art-recognized technique of random mutagenesis to produce the desired DNA methyltransferase. Applicant argues that the examiner has failed to state why one would not expect to be able to extrapolate from applicant's example across the entire scope of the claims and argue that nothing more than routine experimentation is required to make the claimed invention, asserting that to make the invention, one need only a set of primers for random mutagenesis. Applicant's argument is not found persuasive.

Contrary to applicant's assertions, undue experimentation is required to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass all chimeric proteins comprising any DNA methyltransferase having any mutation that confers attenuated DNA binding activity and any DNA binding protein that will bind to any gene promoter sequence, wherein the chimeric protein has the ability to inhibit target gene expression. It is noted that the scope of the claims encompasses not only those DNA binding proteins that are naturally-occurring, but further encompasses any mutants and variants thereof.
- The lack of guidance: The specification fails to provide sufficient guidance to enable the claimed invention. While the specification provides a method for generating the claimed chimeric protein, there is no evidence of record that, at the time of the invention, such a method would have resulted in a chimeric protein having the desired activity. Furthermore, while the specification asserts "the procedure [for obtaining a desired mutant methyltransferase] is rapid" (page 42, lines 14-15), the specification fails to provide guidance as to the rate of success in a "rapid" amount of time. As such, it is unclear as to whether a few days or a few years – if ever – is required to obtain a clone encoding the desired chimeric protein.

Therefore, a skilled artisan would have no assurance of success that, by practicing the screening methods as set forth in Examples 1 and 3 of the specification, the desired chimeric protein can be generated.

- The lack of a working example: While MPEP § 2164.02 acknowledges that a working example of the claimed invention is not required, it also acknowledges that "[l]ack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." As stated above, the specification fails to disclose even a SINGLE example of the claimed invention and therefore fails to provide any assurance of success of generating the desired chimeric protein. Instead, the specification relies upon the skilled artisan to perform further experimentation in the form of trial and error screening methods to arrive – if ever – at a chimeric protein having the desired characteristics (see Examples 1 and 3 of the specification).
- The high level of unpredictability in the art: There is a high degree of unpredictability in making the claimed chimeric protein. While applicant asserts that only routine experimentation is required to make and use the claimed invention, there is no evidence of record that at the time of the invention a skilled artisan would have any assurance of success of generating such a chimeric protein. Furthermore, the disclosed method of making the claimed chimeric protein is, as acknowledged by the specification, "random" (see, e.g., Example 1), because, as the specification states, "[i]t cannot be predicted as to which mutations might give the desired reduction in affinity for DNA" (page 40, lines 10-11). The unpredictability is further evidenced by the specification, which states, "[i]f clones of the desired binding and enzymatic specificity do not emerge from the screen, a likely reason may be stearic incompatibility of the DNA binding protein and DNA methyltransferase in the orientation shown in Figure 6. New constructs may be made in which the order of the moieties are reversed, and the selection screen described above may be done on these new constructs" (page 42, lines 4-10). While the specification suggests that the experimentation is "not demanding", there is no reasonable expectation of success – particularly in view of the lack of even a single working example – that the desired chimeric protein can be made. MPEP § 2164.02 states, "[t]he 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily

anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art." In this case, one of skill in the art cannot readily anticipate the effect of a change, i.e., mutation, within the components of the chimeric protein with an expectation of obtaining a chimeric protein having the desired biological characteristics. Such unpredictability is evidenced by the prior art. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability" (page 247).

- The amount of experimentation required is undue: While methods of generating variants of a polypeptide were well known in the art at the time of the invention, e.g., random mutagenesis, it is not routine in the art to screen for all chimeric proteins comprising a DNA methyltransferase/DNA binding protein having any number of substitutions or modifications as encompassed by the instant claims with the ability to bind to any target gene's promoter and inhibit expression of said target gene. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Regarding mutations of a DNA binding protein, applicant argues that to the extent the claimed chimeric protein comprises a known DNA binding protein with known specificity such as LexA, the rejection is without merit since the specification need not teach that which is known in the art. Applicant's argument is not found persuasive.

In this case, applicant's argument is not commensurate in scope with the claims as the claims are not so limited to a particular DNA binding protein having specificity for any particular DNA binding sequence, i.e., none of the claims is limited to a chimeric protein comprising a naturally occurring LexA protein as the DNA binding protein moiety of the chimeric protein. Instead, the claims broadly encompass any DNA binding protein (e.g., claim 1), any zinc three-finger DNA binding protein (e.g., claim 4), or any mutant LexA protein (e.g., claim 5) having specificity for any promoter sequence. The claims encompass mutants and variants of naturally-occurring DNA binding proteins, particularly in view of the specification, which teaches a trial and error method for obtaining a DNA binding protein having the desired characteristics (see Example 3, pages 44-47 of the specification).

Regarding mutations of a DNA binding protein, applicant argues that to the extent the claimed chimeric protein comprises a mutant DNA binding protein, applicant argues that methods of making such DNA binding proteins were known in the prior art, citing Desjarlais et al., Rebar et al., and Wu et al. (cited in the IDS filed March 30, 1998) as evidence of such, and the specification need not teach that which is known in the art. Applicant argues that the guidance given in Example 3 sufficiently enables a skilled artisan to make the claimed invention. Applicant's argument is not found persuasive.

It should be noted that the prior art references cited by applicant teach methods of making zinc finger DNA binding proteins that recognize a specific, predetermined DNA sequence. However, with the exception of claim 4, the claims are not limited to a zinc finger protein and the claims do not limit the promoter sequence to a known sequence and instead encompass DNA binding proteins that bind to promoters that have yet to be identified. As such, it is unclear as to how the methods of the prior art would be relevant for identifying such promoters with an unidentified nucleotide sequence. Regardless of whether or not the methods were well known in the art, at the time of the invention neither the specification nor the prior art was able to identify even a single working example of the claimed chimeric

protein. Thus, there is no assurance that a skilled artisan, practicing the disclosed method, will obtain a chimeric protein comprising a DNA binding protein having the desired characteristics.

Applicant argues that complex experimentation does not necessarily make it undue if the art typically engages in such experimentation. Applicant argues that random mutagenesis is widely practiced in the art and that Example 1 of the specification provides guidance for using this technique to make the recited methyltransferase, requiring only routine experimentation. Applicants argue that the ability to quickly screen a large number of clones provides a reasonable expectation of success in isolating a desired clone. Applicant argues that the quantity of experimentation needed to make the claimed invention is not large, and even if it were, it would not be undue. Applicant's argument is not found persuasive.

There is no dispute that random mutagenesis is a technique that was widely practiced in the art at the time of the invention. Contrary to applicant's assertion, based on the teachings of the specification, there is no reasonable expectation of success in obtaining the desired chimeric protein. While there is no dispute that random mutagenesis was a technique that was widely used in the art at the time of the invention, the specification fails to provide guidance that such a method would successfully produce the desired chimeric protein. Applicant's assert a large number of clones can be screened "quickly", however, at the time of the invention, there was no assurance of success that the disclosed method would generate the desired chimeric protein. Applicant asserts that only a few days is required to screen 10^9 clones. However, the specification fails to provide guidance as to the rate of success, i.e., how many clones encoding a chimeric protein having the desired characteristics can be obtained out of the 10^9 clones – if any at all? Thus, it is unclear as to whether a few hours, days, or years is required – if ever – to obtain a clone encoding the desired chimeric protein. As stated above, there is a high level of unpredictability in making the claimed chimeric protein, particularly in view of the lack of even a single working example. There is no assurance of success in making the claimed chimeric protein. In this case, the specification provides no more than a starting point for further research and at most enables a skilled artisan how to attempt to discover the claimed invention.

Even if the specification enables the claimed chimeric protein, the enablement rejection of claims 44-46 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The examiner maintains his position that the specification fails to enable the claimed invention. In this case, undue experimentation is required to make the claimed invention.

Applicant argues that the examiner has not provided a reasonable basis to question the enablement of the claimed "pharmaceutical compositions". Applicant's argument is not found persuasive.

The examiner maintains that the specification fails to provide sufficient guidance for making and using the claimed pharmaceutical composition. The specification fails to identify any specific disease that can be treated, prevented, or ameliorated by the claimed pharmaceutical composition, which is undisputed by applicant. Also, the specification fails to identify a specific route of administration and dosage required for treating, preventing, or ameliorating a particular disease. Such guidance is clearly required to make and use the claimed invention. Also, the prior art acknowledges the unpredictability of using DNA-methylation induced gene silencing as a treatment (see page 9 of the Office action mailed November 05, 2002) – which again is undisputed by applicant. Furthermore, at the time of the invention, gene therapy as a treatment was highly unpredictable as evidenced by Dang et al. (*Clin Cancer Res* 5:471-474), who teach, "[t]his committee found human gene therapy to be an immature science with limited understanding of gene regulation and disease models for pre-clinical studies" (page 471, left column). As such, undue experimentation would be required to make and use the claimed pharmaceutical composition.

Conclusion

[9] Status of the claims:

- Claims 1-8, 10-15, 18, 24-26, and 42-46 are pending.
- Claims 1-8, 10-15, 18, 24-26, and 42-46 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are

unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

03-09-04